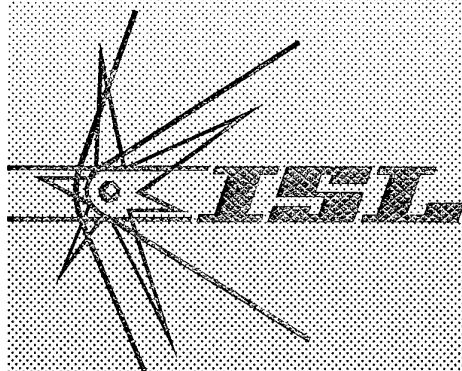


Fr 230



INSTITUT FRANCO-ALLEMAND DE RECHERCHES DE SAINT-LOUIS
DEUTSCH-FRANZÖSISCHES FORSCHUNGSMSTITUT SAINT-LOUIS

SAINT-LOUIS (Haut-Rhin) - 5 rue du Général Cassagnou
Tél. 03 89 69 50 00 - Téléfax 03 89 69 50 02

Adresse postale : F 68301 SAINT LOUIS CEDEX, BP 34
Postanschrift: D 79574 WEIL AM RHEIN 1, Postfach 1260

Treatment of Noise-Induced Hearing Loss

GERVAIS-D'ALDIN CH., CHERNY L.*, DANCER A.

*Otolaryngology Dept., Hadassah Medical Organization, Jerusalem, Israel

7th International Congress on Noise as a Public Health Problem
(NOISE EFFECTS '98), Sydney, Australia, 22-26 November 1998

Diese Unterlagen dürfen ohne ausdrückliche Genehmigung
des Bundesministeriums der Verteidigung - Rü VII 6 -
nur an Bundeswehrrdienststellen oder militärische Stellen
anderer NATO-Staaten weitergegeben werden.

Axe de recherches
Schwerpunkt

212

PU 324/99

DTIC QUALITY INSPECTED 4

20000926 044

71

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE 1999	3. REPORT TYPE AND DATES COVERED International Congress Report, 22-26 November 1998	
4. TITLE AND SUBTITLE Treatment of Noise-Induced Hearing Loss			5. FUNDING NUMBERS 71	
6. AUTHOR(S) Ch. G. d'Aldin [1], L. Cherny [2] and A. Dancer [1]				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) [1] Physiology Group, French-German Research Institute of Saint-Louis, BP 34, 68301 Saint Louis, France [2] Otolaryngology Dept., Hadassah Medical Organization, PO Box 1200, 91120 Jerusalem, Israel			10. SPONSORING/MONITORING AGENCY REPORT NUMBER PU 324/99	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Institu Franco-Allemand De Recherches De Saint-Louis 5 Rue du G2en2eral Cassagnau BP34 - 68301 Saint-Louis Tel: 3 89 69 50 00 Email: isl@cedocar.fr Fax: 03 89 69 50 02				
11. SUPPLEMENTARY NOTES Text in English.				
12a. DISTRIBUTION/AVAILABILITY STATEMENT DTIC Users Only.			12b. DISTRIBUTION CODE	
ABSTRACT (Maximum 200 words) The actual efficiency of the present medical treatments of the acoustic trauma is investigated. Guinea pigs are subjected to an acoustic trauma. The recovery of the noise-induced hearing loss is followed up to 14 days post exposure by electrocochleography and morphologic examination of the cochlea is performed (scanning electron microscopy). When corticoids are administrated one hour after the noise exposure, less threshold shift and less hair cell damage are observed.				
14. SUBJECT TERMS German, French, STI, Noise, Hearing, Acoustics, Trauma			15. NUMBER OF PAGES 8	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT UNCLASSIFIED	18. SECURITY CLASSIFICATION OF THIS PAGE UNCLASSIFIED	19. SECURITY CLASSIFICATION OF ABSTRACT UNCLASSIFIED	20. LIMITATION OF ABSTRACT UL	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

TREATMENT OF NOISE-INDUCED HEARING LOSS

Ch. G. d'ALDIN [1], L. Cherny [2] and A. Dancer [1]

[1] Physiology Group, French-German Research Institute of Saint-Louis, BP 34,
68301 Saint-Louis, France

[2] Otolaryngology Dept., Hadassah Medical Organization, P.O. Box 1200,
91120 Jerusalem, Israel

Abstract

The actual efficiency of the present medical treatments of the acoustic trauma is investigated. Guinea pigs are subjected to an acoustic trauma. The recovery of the noise-induced hearing loss is followed up to 14 days post exposure by electrocochleography and morphologic examination of the cochlea is performed (scanning electron microscopy). When corticoids are administrated one hour after the noise exposure, less threshold shift and less hair cell damage are observed.

TREATMENT OF NOISE-INDUCED-HEARING LOSS

Ch. G. d'Aldin [1], L. Cherny [2] and A. Dancer [1]

[1] Physiology Group, French-German Research Institute of Saint-Louis, BP 34,
68301 Saint-Louis, France

[2] Otolaryngology Dept., Hadassah Medical Organization, P.O. Box 1200,
91120 Jerusalem, Israel.

1. INTRODUCTION

Intense sound stimulation results in structural changes leading to functional auditory impairment. Intense sound stimulation induces two major types of damage: 1) injuries occurring first in the first row of the outer hair cells (OHCs), then in the inner hair cells (IHCs) and in the second and the third rows of OHCs [1], and 2) a massive destruction of dendrites of the primary auditory neurons below the IHCs [2,3]. After an acoustic trauma (intense continuous noise), the acute hearing losses are due both to hair cell injuries and to dendrite damage [4]. Synaptic repair can occur in 5 days [5] but most hair cell damage remains, which is probably responsible for the long-term threshold shifts. Therefore, it is essential to treat patients who undergo acoustic trauma by addressing both the hair cell injuries and the dendrite damage.

Due to the variability of the functional losses and of the treatments presently used, due to the ignorance of the pre-exposure hearing condition and of the parameters of the noise exposure, the efficiency of the present medical treatments of the acoustic trauma is very difficult to assess in man. It is also difficult to estimate which part of the functional recovery is due to the treatment, and it is impossible to assess the morphological changes at the level of the organ of Corti.

The aim of this study is to assess the actual efficiency of the main medical treatments of the acoustic trauma by using a well-standardised animal study. The effects of the acoustic trauma are evaluated by electrocochleography, and by the direct observation of the hair cells (scanning electron microscopy).

2. MATERIAL AND METHODS

Pigmented guinea pigs (300-350 g) free of middle-ear infection are anaesthetised. The bulla is opened to expose the cochlea. A recording electrode is put on the round

window. The bulla is reclosed and the recording electrode and the reference electrode are soldered to a plug fixed on the skull. Finally, the surgical wound is sutured and animals are left to recover from the surgical operation for 3 days.

Functional evaluation: tone bursts with a 1 ms rise/fall time (12.5 ms duration) are generated by a Tucker Davis system and presented (8/s) in free field. The frequencies are 2, 2.8, 4, 5.6, 8, 9.5, 11.3, 13.4, 16, 19, 22.6 and 32 kHz. CAP thresholds can be recorded either in awake or in anaesthetised animals.

Acoustic trauma: three days after the surgical preparation, the animals are anaesthetised and a pre-exposure audiogram is performed. Immediately after, the animals are exposed to 1/3 octave band noise centred on 8 kHz at 129 dB SPL during 20 minutes. Twenty minutes after the end of stimulation another audiogram is performed to obtain the short-term threshold shift. Long-term threshold shift is measured at days 1, 2, 3, 7 and 14 in awake guinea pigs.

Morphological observations: after the last audiogram (14 days) the animals are deeply anaesthetised. The cochlea is taken, fixed and sent to the Hadassah University Hospital for SEM observation. The organ of Corti is thoroughly analysed with respect to damage to the stereocilia of the inner and outer hair cells. Stereocilia damage is defined according to Borg [6]: (i) destroyed: a total loss of the stereocilia bundle, (ii) damaged: more than 10% disarray, fall or loss of the stereocilia (corresponding to "altered stereocilia" in Borg classification and to a grade 1, 2 in Fredelius scale [7]). Cochleograms represent the percentage of intact, damaged and destroyed hair cells every 200-micrometer (corresponding approximately to 20 IHCs) from 2 to 10 mm from the base (first and a half turn).

3. MEDICAL TREATMENTS

For each group of animals ($n=10$), the treatment begins 1 hour after the end of the sound exposure and lasts for 5 days.

Carbogen therapy: a carbogen mixture (7% carbon dioxide and 93% oxygen) is delivered at ambient pressure and at a constant flow rate for 30 minutes., twice a day.

Oxygen therapy (ambient pressure): pure oxygen is delivered at ambient pressure and at a constant flow rate for one hour, twice a day.

Hyperbaric oxygen therapy: animals are placed in a pressure chamber. The chamber is pressurised at 2.5 ATA or 1.5 ATA with 100% oxygen. The pressure is held for 1 hour, twice a day.

Corticoid therapy: methylprednisolone hemisuccinate (Solu-Medrol®, Upjohn) 2, 20, 40, 100 or 200 mg/kg is given once a day by intramuscular injection.

Combined hyperbaric oxygen-corticoid therapy: animals receive corticoids (20 mg/kg) and breathe hyperbaric oxygen (2.5 ATA).

4. RESULTS

Functional and Morphological Correlation

To compare the threshold shifts and the cochlear damage, the audiograms and the cochleograms are scaled to adjust the distance from the base of the cochlea to the

frequency. In some animals, threshold shifts and cochlear damage correlate well. However in some other animals, despite the complete recovery of the threshold shifts, important morphological damage to the stereocilia can be observed.

Medical Treatments of the Acoustic Trauma

Carbogen therapy: no significant difference for audiograms can be observed between controls and carbogen treated animals (Figure 1 and 2).

SEM observations indicate that hair cell damage is maximal between 3.5 and 6.5 mm from the base of the cochlea (CF from 13,4 kHz to 8 kHz) (Figure 2).

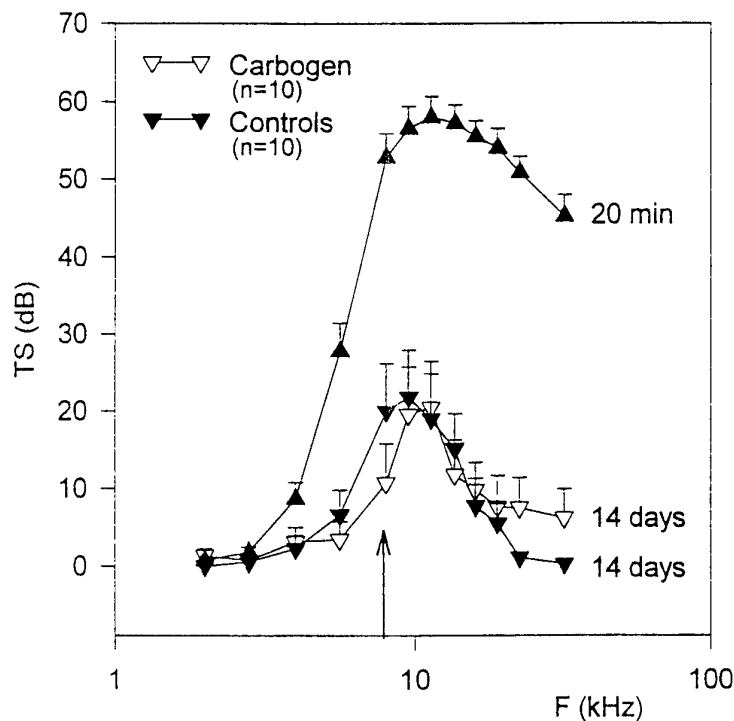


Figure (1): CAP threshold shifts in dB (mean values and SD) recorded immediately after and 14 days after the acoustic trauma in controls and in carbogen treated animals

Oxygen therapy: when oxygen is delivered at ambient pressure, no significant difference can be observed between controls and treated animals either for audiograms or for cochleograms.

Hyperbaric oxygen therapy (2.5 ATA): at day 14, threshold shifts are higher than in the control group (40 dB instead of 20 dB). These results are statistically significant ($0.001 < p < 0.01$). Cochlear damage is larger than for the controls: inner and all three rows of outer hair cells are heavily damaged (Figure 2). The same kind of results is observed with hyperbaric oxygen therapy using 1.5 ATA.

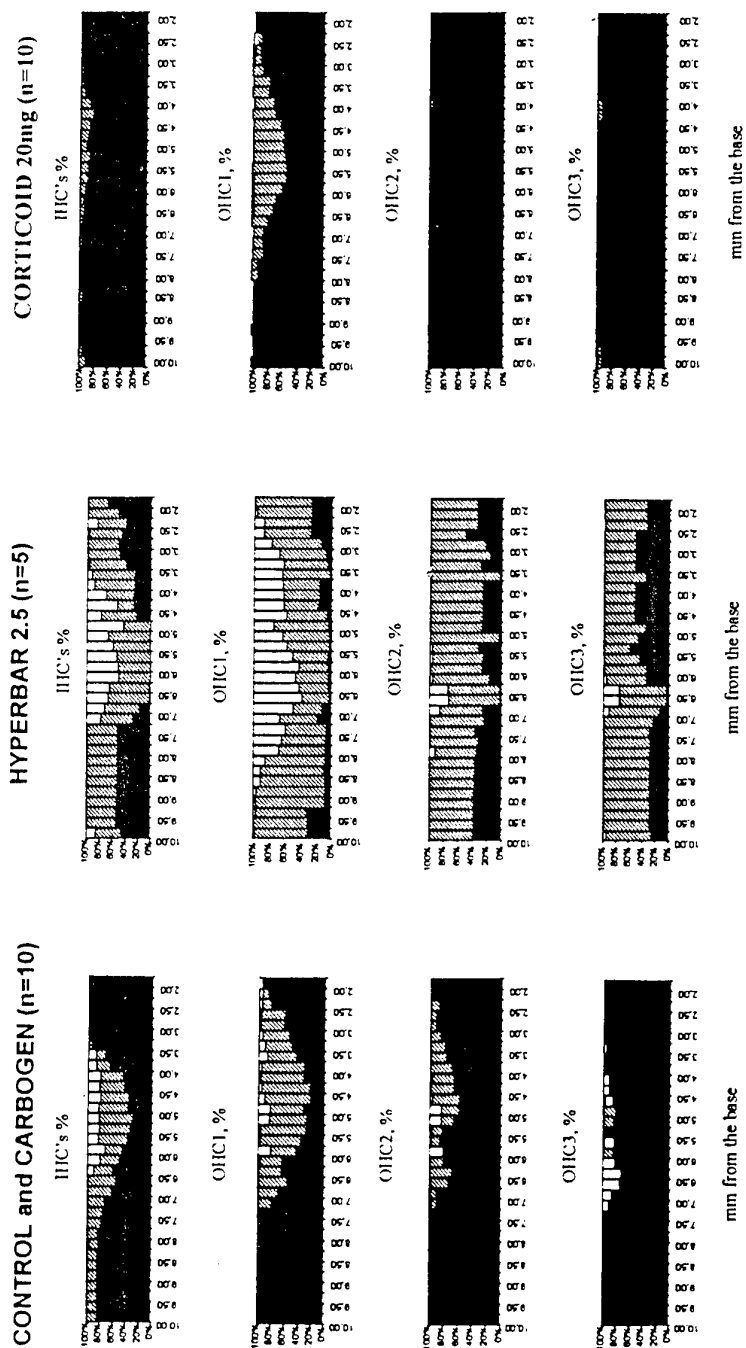


Figure (2): Cochlear damage 14 days after the acoustic trauma: (i) Carbogen treated animals, (ii) Hyperbaric Oxygen treated animals (2.5 ATA), (iii) Corticoid treated animals (20mg/kg) (white: destroyed cells, hatching: damaged cells, black: intact cells)

Corticoid therapy: when the animals are treated at once (and during five days) with doses of 20 mg/kg, the recovery of the threshold shift is significantly improved as well 1 day as 14 days after the exposure (maximal TS: 25 dB instead of 38 dB on the 1st day, and 10 dB instead of 20 dB on the 14th day). Cochlear damage observed at day 14 in the treated animals is smaller than in the controls and is restricted at the first row of the outer hair cells and at the inner hair cells (Figure 2). Corticoid therapy (20 mg/kg) improves significantly the functional and morphological recovery. Moreover, combined hyperbaric oxygen-corticoid therapy improves significantly the functional and morphological recovery (data not shown).

4. DISCUSSION

In some animals the functional recovery (assessed by CAP audiograms) is complete but morphological damage remains. Therefore in man, apparent complete functional recovery (assessed by behavioural audiometry) does not exclude the possibility of stereocilia damage. In case of further exposures, this damage could account for a higher sensibility to acoustic trauma and more rapid tendency to presbycusis.

These preliminary results indicate that among the medical treatments presently prescribed in man, only corticoid therapy improves functional and morphological recovery after acute acoustic trauma. When used alone, the other treatments: namely carbogen, oxygen at ambient pressure level or hyperbaric oxygen, are either ineffective or ill effective. Unexpectedly, hyperbaric oxygen combined with corticoid therapy improves recovery when compared to corticoid therapy used alone.

Carbogen is considered one of the most powerful vasodilators of cerebral capillary beds. Many studies indicate that carbogen inhalation during noise exposure results in a reduction of NIHL [8]. Brown [9] found significantly less outer hair cell loss in guinea pigs which were given carbogen during a 120 dB broad band noise exposure. However, and as reported by Hatch et al, [10], we observe no significant difference between the carbogen treated animals and the control group. Therefore, carbogen could have a protective effect but almost no curative efficiency.

The idea that inhalation of pure oxygen could be used as medical treatment of acoustic trauma is based on experimental studies performed by Lamm and Arnold who have shown that high-intensity noise causes cochlear hypoxia which correlates with post exposure hearing loss [11]. However, the same authors showed that noise-induced cochlear hypoxia is not compensated by oxygen delivered at ambient pressure level [12]. Moreover, improvement in threshold shifts is only reported when pure oxygen is given during noise exposure [10]. Accordingly, the effectiveness of oxygen delivered at ambient pressure level after intense noise exposure is not apparent in our study.

The aim of hyperbaric oxygen administration is to significantly improve partial oxygen pressure in inhaled air. At 2 ATA, the available amount of oxygen and the blood dissolved oxygen fraction are multiplied by 10 [13]. However, in our study hyperbaric oxygen treatment induces higher threshold shifts and additional hair cells damage. Together with the fact that this treatment induces barotrauma in up to 50% of the human patients (Probst, 1998), that suggests that hyperbaric oxygen should not be used alone as an acute treatment of the acoustic trauma.

When corticoid is administrated one hour after the noise exposure, less threshold shift and less hair cell damage are observed [12]. One hypothesis put forward by Lamm and Arnold is that the activation of the enzyme Na,K-ATPase by corticoid may contribute to restoration of disturbed cellular osmolality, electrochemical gradients, and neuronal conduction. Actually, it seems that corticoids act both at the dendritic and the cellular level [4,5]. However, corticoids induce oxygen consumption to mobilise amino acid for glucogenesis and alter glucose utilisation by oxygen consuming mechanisms. Therefore, improving partial oxygen pressure in inhaled air could compensate the decline of partial oxygen pressure and potentiate the corticoid effect. Our first results indicate that combined corticoid and hyperbaric therapies significantly improve functional and morphological recovery.

REFERENCE

- [1] Saunders JC, Dear SP, Schneider ME (1985). The anatomical consequences of acoustic injury: A review and tutorial. *J. Acoust. Soc. Am.* 78, 833-860.
- [2] Spoendlin H. (1971). Primary structural changes in the organ of Corti after acoustic overstimulation. *Acta Oto-Laryngol.* 71, 166-176.
- [3] Pujol R, (1991). Sensitive developmental period and acoustic trauma: Facts and hypotheses. In A. Dancer, D. Henderson, RJ. Salvi and RP. Hamernik (Eds.), *Noise-Induced Hearing Loss*. St. Louis, MO: Mosby Year Book, 196-203.
- [4] d'Aldin C., *et al.* (1995). Effects of a dopaminergic agonist in the guinea pig cochlea. *Hear. Res.* 90, 202-211.
- [5] Puel JL *et al.* (1995). Synaptic regeneration and functional recovery after excitotoxic injury in the cochlea. *C.R. Acad. Sci., Série III.* 318, 67-75.
- [6] Borg E, Canlon B, Engstrom B (1995). Noise - induced hearing loss. *Scandinavian audiology*, 24, Suppl. 40. [7] Fredelius L. *et al* (1987). Qualitative and quantitative changes in the guinea pig organ of Corti after pure tone acoustic overstimulation. *Hear. Res.* 30, 157-168.
- [8] Witter HL., Deka RC, Lispcomb DM, Shambaugh GE (1980). Effects of prestimulatory carbogen inhalation on noise-induced temporary threshold shifts in humans and chinchillas. *Am. J. Otol.* 1, 227-232.
- [9] Brown JJ., M.B. Meikle MB, Lee CA (1985). Reduction of acoustically induced auditory impairment by inhalation of carbogen gas (temporary pure-tone induced depression of cochlear action potentials). *Acta Otolaryngol.* 100, 218-228.
- [10] Hatch M, *et al.* (1991). The effects of carbogen, carbogen dioxide, and oxygen on noise-induced hearing loss. *Hear. Res.* 56, 265-272.
- [11] Lamm K, Arnold W (1996). Noise-induced cochlear hypoxia is intensity dependent, correlates with hearing loss and precedes reduction of cochlear blood flow. *Audiol. Neurotol.* 1, 148-160.
- [12] Lamm K, Lamm C, Arnold W (1998). Effect of isobaric oxygen versus hyperbaric oxygen on the normal and noise-damaged hypoxic and ischemic guinea pig inner ear. *Adv. Otorhinolaryngol.* Basel, Karger. 54, 59-85.
- [13] Fernault J, Hirsch B, Derkay C (1992). Hyperbaric oxygen therapy: effect on middle ear and Eustachian Tube function. *Laryngoscope.* 102, 48-52.